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(54) Title: WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE

(57) Abstract

Water-soluble pressure-sensitive adhesives include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are solid at room temperature and have a hydrophilicity as measured by water uptake greater than about 25 %. Suitable plasticizers are liquid at room temperature and having a boiling point higher than about 80 °C. The adhesives according to the invention may conveniently be provided in dry film form. Preferred water-soluble pressure-sensitive adhesives of the invention adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining, and adhesive films of the invention are useful as denture adhesives. For use in the oral cavity preferred adhesives of the invention are made of GRAS- or NF-certified materials.

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WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE

TECHNICAL FIELD

This invention relates to mucoadhesives, and particularly to compositions that adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining.

BACKGROUND ART

Various bioadhesives have been proposed for use in establishing adhesive contact with mucosal surfaces.

For example, U.S. Patent No. 4,713,243 describes an extruded film for use in controlled release of medicaments, including a water-soluble or swellable polymer matrix capable of adhering to a wet mucous surface, made up of 40 - 95 % hydroxy propyl cellulose, 5 - 60 % poly(ethylene oxide), optionally up to 10 % of a water-insoluble polymer (ethyl cellulose, propyl cellulose, polyethylene or polypropylene) and 2 - 10 % of a plasticizer introduced to facilitate processing, and containing the medicament. There is no disclosure in the '243 patent that such compositions can adhere to materials that may be used in oral prosthesis or other devices, or that they are pressure-sensitive.

U.S. Patent No. 4,948,580 describes a bioadhesive composition for delivery of anti-bacterials, including a copolymer of ("PVME/MA"), and gelatin, dispersed in an ointment base.

Adhesives for affixing dental prostheses in the mouth are conventionally in the form of pastes or creams. These are messy and inconvenient to use, and generally adhere poorly or not at all after extended periods.

U.S. Patent No. 4,529,748 describes a dental prosthesis adhesive in powder form, in which the particles are made from carboxy methyl cellulose, poly(ethylene oxide), poly(acrylic acid), and karaya gum. Some portion of the particles are coated with a cellulose or acrylate polymer film that dissolves slowly in saliva.

SUMMARY OF THE INVENTION

We have discovered water-soluble pressure-sensitive mucoadhesives that additionally adhere to a variety of materials, such as polymers, that can be used in construction of devices for emplacement on a mucosal surface or within a body cavity that has a mucosal lining. The adhesives require no moistening prior to contact with the mucosal or the polymer surface. Water-soluble pressure-sensitive mucoadhesive films according to the invention can be used, for example, to affix a dental plate within the mouth.

Or for example, water-soluble pressure sensitive films according to the invention can constitute the adhesive layer of a laminated mucoadhesive device for emplacement in a mucosa-lined body cavity and delivery of one or more active substances into the body cavity, in which additional layers or layers, also soluble in the fluids bathing the surface of the body cavity, contain the active substance or substance to be delivered.

In one general aspect, the invention features a layered composite mucoadhesive device for delivery of an active substance into the oral cavity, having an active-containing layer that includes the active substance dispersed or dissolved in a water soluble polymer, and a water soluble adhesive layer.

In some embodiments the active-containing water soluble polymer layer is a hydrophobic material that will n t dissolve in cold water (below about 40°C)

and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

The rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component: a given polymer type dissolves or disperses more slowly at higher molecular weights than at lower molecular weights. In some embodiments the active-containing layer includes a polymer such as hydroxypropyl cellulose, and may additionally include a plasticizer such as glycerin. In a particular embodiment, hydroxypropyl cellulose (HPC Klucel LF), having a molecular weight of 80,000, with glycerin as a plasticizer, is useful.

Any of a variety of active substances may be delivered using devices constructed according to the invention. Such active substances are well known to those of skill in the art to which this invention pertains. For relief of sore throat pain, for example, substance such as benzocaine, lidocaine, dyclonine and the like, which are available over the counter or in syrup or tablet form, may be used. For relief of cough, substances such as detromethorphan IIBr, nosepine, codeine phosphate, methol, and the like may be used. Suitable odorants and flavorants include, for example, mint odorants and fruit flavorants such as citrus flavorants, cherry flavorants, and the like. Reference is made to G. Reineccius, ed. *Source Book of Flavors*, Chapman & Hall.

For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

The pressure-sensitive adhesives f the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities.

Consequently, the adhesive eventually dissolves completely within the body cavity in which they are placed, and is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal.

DISCLOSURE OF THE INVENTION

Accordingly, in one general aspect, the invention features a water-soluble pressure-sensitive adhesive including a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are characterized as being solid at room temperature (that is, as having a glass transition temperature T(g), or melting point T(m), higher than about 25°C, and more preferably higher than about 30°C, and lower than about 120°C, and more preferably lower than about 100°C); and having a hydrophilicity as measured by water uptake greater than about 25 %. Suitable plasticizers are characterized as being liquid at room temperature and having a boiling point higher than about 80°C.

Suitable polymers include polysaccharides such as for example cellulose-type materials and natural gums, polypeptides, and water-soluble synthetic polymers. Particular examples of such suitable polymers which are GRAS certified include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934 (B.F. Goodrich), starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In some embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, as well as to human skin.

In other embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k.

In another general aspect, the invention features a water-soluble pressure-sensitive adhesive film made up of a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In preferred embodiments the thickness of the film is in the range of about 5 - 20 mils, and is shaped to fit and to conform generally to a mucosal surface-contacting portion of a dental prosthesis such as a dental plate. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Such a film can be used as a denture adhesive, that can adhere to oral mucosal surfaces and to dental prosthesis for an extended period, typically f m re than about 5 hours. The film can be

used as part of a system for delivery of substances through the oral mucosa (as a buccal transmucosal patch), or for delivery of substances into the oral cavity itself.

In another general aspect, the invention features a laminated mucoadhesive device for emplacement on a mucosal surface, such as on a surface within a body cavity that has a mucosal lining, which device has a first layer made up of a water-soluble pressure-sensitive adhesive as described herein and a second water-soluble layer containing the active substance. As the active substance-containing layer dissolves or otherwise disperses within the fluids bathing the surface of the body cavity, the active substance is released into and is carried by the fluids.

In some embodiments the laminated device includes two or more water soluble active substance-containing layers. Each of the layers may contain a different active substance or combination of active substances, for example; or they may contain the same active substance but in differing amounts. The different active substance-containing layers may dissolve or disperse at different rates in the fluids of the body cavity, so that the rate of release of the active substance or active substances may vary over time.

In preferred embodiments the active substance includes a flavorant or deodorant or reordorant and is useful in the body cavity as a deodorant or odor masking agent, for example as a breath freshener in the oral cavity; or it includes an antibacterial or antifungal agent, useful in the body cavity to treat enfection or to prevent formation of odor; or it includes an anaesthetic or analgesis, useful in the body cavity to treat pain.

Description of Preferred Embodiments

BEST MODE FOR CARRYING OUT THE INVENTION

Modes of Carrying out the invention

1. Preparati n of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software package (Stable Micro Systems, Ltd.), as follows. A sample of the film on a release liner is mounted upon a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by submersion of a sample of the film in water at 21°C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes.

2. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, f 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 0F to a

thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

3. Preparation of dental prosthesis adhesive film.

A water-soluble pressure-sensitive adhesive film made as described above can be die-cut in a shape that conforms to that portion of the dental prosthesis that closely fits the mucosal surface of the mouth, such as the part of the dental plate that fits against the palate. The shaped film pieces can be packaged dry. For use, the dry film is pressed onto the appropriate surface of the dental prosthesis so that it adheres. Then the dental prosthesis with the adhesive affixed is inserted into the correct position in the mouth and pressed against the mucosal surface until adhesion is achieved.

The following Examples are intended to illustrate but not to limit the invention.

EXAMPLES

Example I

Breath Freshening Device

A dissolvable mucoadhesive device capable of releasing a flavor into the oral cavity was constructed as follows: A solution was made up by co-dissolving 15.4 grams of polyvinyl pyrrolidone PVP (K90) and 6.0 grams of glycerin in 80 grams of isopropanol (IPA). The resulting solution was coated at a thickness of 30 mils onto a polyester release liner and allowed to dry for 15 hours at room temperature. The resulting dry film was tacky at room temperature and had a final thickness of about 5 mils. A second solution containing 43 grams of IPA, 42 grams of water, 15 grams of HPC EF, 2.5 grams of peppermint oil and 3.0 grams of NutrasweetÔ brand sweetener containing aspartame was prepared by mixing all the components until fully dissolved. The solution was then coated at a thickness

of 50 mils onto a polyester release liner. The film was allowed to dry at room temperature for 15 hours to a final thickness of about 5 mils.

The two dry films were laminated together. Discs having a diameter of about 1.2 cm were cut from the laminate. The discs were tested *in vivo* by adhering a single disc to the upper palate of three volunteers. The discs adhered well to the mucosal surface and upon hydration with saliva immediately began releasing peppermint oil and aspartame as noticed by taste. The total time of dissolution in the mouth was about 10 minutes, during which time a pleasant, refreshing mint flavor was perceived.

Example II

Adhesive Layer Optimized for High Tack and long Dissolution Time.

In this example, adhesive layer compositions having various selected proportions of PVP, HPC, and Glycerol were tested both for peak tack and for time required to complete dissolution, in order to determine both the relative contribution each of these components makes to the tack and dissolution time characteristics of the adhesive, and to determine the ranges within which the proportions of these components preferable are provided, to provide adhesives having good tack and dissolution time characteristics.

The adhesive layers were constructed by blending HPC, PVP and Glycerin in the selected proportion, and pressing the resulting mixture in a heated Carver laboratory press at 200 F. to a thickness about 35 mils.

Peak tack was tested on adhesive disks having 10 mils thickness, using a TA.XT2 Texture Analyzer, with a Plexiglas probe having a diameter 8mm, advanced to the surface at 1 mm/sec to a force threshold of 20 grams, then advanced at a penetration rate of 0.1 mm/sec to a penetration depth of 0.5 mm, held for 10 seconds at a contact force of 125 grams, and then withdrawn at 1 mm/sec.

Time to complete dissolution was measured by affixing an adhesive disc to the inner wall of a vial containing 100 ml nanopure water at room temperature and stirring the water at 250 rpm.

The results are shown in Table I.

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TABLE I

Reference	HPC (%)	PVP (%)	Gly (%)	Tack (g)	Diss. Time (min)
319-099	20	38	42	403±62	28.3±2.6
319-100	33	32	35	478±41	53.2±10.5
319-101	13	52	35	749±112	26.2±6.1
319-102	13	32	55	516±64	31.8±4.2
319-103	20	38	42	410±67	32.1±6.3
319-104	33	32	35	425±32	50.2±7.4
310-105	13	52	35	815±161	22.2±2.6
310-129	20	30	50	527±46	56.7±4.0
310-130	10	45	45	572±64	25.0±6.4
310-131	30	30	40	526±101	58.6±4.0
310-132	20	45	35	405±59	38.9±13.0
298-85	33	30	37	388±70	64.7±20.6
298-86	33	25	42	585±88	77.0±11.1
310-108-2	16	47	37	584±117	39.4±18.4
310-120-2	16	44	40	492±143	27.0±9.07
310-124-2	16	41	43	511±102	24.6±5.3

In a first step, samples appearing in Table I as Reference Nos. 310-108-2, 310-120-2, and 310-124-2 were f rmulated and tested. The data for tack

and dissolution time for these samples were then analyzed and the resulting analysis was used to select compositions for additional formulation and testing.

The selected compositions appear in Table I as Reference Nos. 310-129, 310-130, 310-131, and 310-132, and Reference Nos. 319-099, 319-100, 319-101, 319-102, 319-103, 319-104, and 319-105.

The data for tack and dissolution time for these selected compositions were then further analyzed to provide ranges for optimization, and two such optimized compositions were selected and tested. These are numbered 298-85 and 298-86 in Table I.

The results were analyzed to rank the variables according to their effect on the tack and dissolution characteristics. The concentration ranges (weight %) that were considered were HPC: 13%-43%; PVP: 32%-52%; Glycerine: 35%-55%.

Taken alone within broad limits, varying PVP had much the greatest effect on tack, followed by HPC; varying Glycerin within broad limits had relatively little effect on tact. Tack was apparently highly affected by variations in HPC and PVP together, and less by variations in PVP and Glycerin together.

Taken alone and within broad limits, varying either HPC or PVP had a significant effect on dissolution time; varying Glycerin within broad limits had relatively little effect on dissolution time.

Generally, for broad range in Glycerin and HPC contents, dissolution time increases at PVP concentrations less than about 34% by weight. Also generally, for a broad range of HPC (particularly above about 20%, more particularly above about 30%, by weight) and Glycerin contents, tack increases at PVP concentration either less than about 35% by weight or greater than about 44% by weight. On this analysis, therefore, optimized tack and dissolution times are expected for compositions having less than about 34% by weight PVP, and above about 20% (more preferable above about 30%) by weight HPC.

Example III

Device for Relief of Sore Throat Pain

A medication-containing mucoadhesive laminated disc according to the invention can be made by forming and then laminating an adhesive film and an active substance-containing polymer film generally as follows.

The adhesive layer. A water-soluble adhesive layer can be formed from an adhesive polymer film, according to the following general protocol. First, the polymer (or polymers) and the plasticizer are thoroughly mixed, using where necessary a suitable solvent such as ethyl alcohol. Where a solvent is used, the resulting mixture is then coated on a release liner, and the solvent is allowed to evaporate to produce a dry film. Dry film samples are then collected and pressed to the desired final film thickness. Where no solvent is used, the mixture can be pressed to a film of the desired thickness.

The active substance-containing layer. First, the polymers and one or more desired active agents and one or more desired flavorants are dissolved, for example by stirring, in an appropriate solvent. Then the resulting thickened solution is formed into a thin (wet) film, for example by casting onto a release liner, and then the solvent is permitted to evaporate to a dry film. Then the dry film is pressed to a desired thickness and is affixed, for example by pressing, onto an adhesive layer prepared as described above.

Hydroxypropyl cellulose (HPC) can be a particularly suitable polymer for construction of the active-containing layer. HPC dissolves completely in aqueous fluids such as the fluids of the oral cavity, and within a selected range of molecular weights, HPC dissolves (or disperses) in the oral cavity sufficiently slowly to provide substantially continuous delivery of the active substance over an extended period. HPC is flexible, so that it conforms well to irregular curved surfaces of the ral cavity; HPC is not tacky when moistened, and has a pleasant

texture in the mouth. It is thus comfortable and unobtrusive for the user. HPC blends well with a variety of active substances.

Glycerol, which may be added as a plasticizer in the active-containing layer, may additionally (or alternatively) act to inhibit crystallization of some active substances that might otherwise occur at the loading concentrations employed (for example, menthol).

Laminated devices are then cut from the laminated film by, for example, die-cutting, to the desired size and shape. Typically, circular or oval shapes may be preferred. The devices can be stored on a release liner affixed to the adhesive surface, and removed from the liner as needed by the user.

A device having a single active substance-containing layer containing a pain-relieving agent such as dyclonine A in amounts sufficient to provide sore throat pain relief initially can have the undesired effect of unpleasantly numbing other tissues in the oral cavity that are adjacent the device while in place, such as the tongue. We have discovered that delivery of the active in two phases can reduce this undesired effect while providing sustained relief from pain.

A preferred device for two-phase delivery of an active substance for relief of sore throat has two active-containing layers, a first layer adjacent the adhesive layer, from which the active is released more slowly over time, and a second layer adjacent the first active-containing layer, from which the active is released more rapidly, over a shorter initial time following placement within the body cavity. Such a configuration provides for an initial burst of the pair-relieving active agent at a suitably high rate to satisfactorily reduce sore throat pain, followed by a sustained release of the active agent at a lower rate suitably high to maintain the effect of pain reduction but not so high as to cause unpleasant numbness in the oral cavity. Accordingly, this invention also provides a method of delivery an active substance to a subject such as a human patient by contacting a device as described herein with a suitable surface of the subject. Suitable surfaces include, but are not limited to a mucosa-lined body cavity such as the ral cavity, the cornea stratum r the skin of the subject.

The two-phase release profile can be achieved either by having the two active-containing layers made from the same polymer (or from similar polymers dissolving or dispersing at about the same rate) but having the active agent present in the lower, sustained release layer at a lower concentration than in the upper, initial burst, layer. Or, the upper layer can dissolve or disperse more quickly in the oral milleu.

In one example for a two-phase delivery of dyclonine, the device is about 0.5 inches in diameter, the layers are made from the same HPC polymer, and the initial release layer can be 5–10 mils thick, and contain 0.25–0.6 milligrams of dyclonine, while the sustained release layer can be 20–25 mils thick, and contain 1–1.5 milligrams of dyclonine. Such a configuration can provide satisfactory throat pain relief within about 1—20 minutes' time, followed by a sustained relief over a time greater than an hour thereafter, while reducing the numbing effect associated with delivery at a constant higher rate.

Other Embodiments

For example, the water-soluble pressure-sensitive adhesives according to the invention can be used to affix transdermal devices to human skin. Because the materials in the adhesive are GRAS certified, they can result in an adhesive product having very low skin irritation and reaction.

The water-soluble pressure-sensitive adhesives of the invention can act as a reservoir for diffusional delivery of a substance into the mucosa-lined body cavity (such as the oral cavity or gastrointestinal tract, or the vaginal cavity), or for delivery of a substance transmucosally through the area of adhesive contact. Preferably for such applications, the adhesive is provided in film form, and is loaded with a suitable quantity of the substance to be delivered. For use in transmucosal delivery, one surface of the adhesive film makes adhesive contact with the mucosal surface; preferably the other surface of the adhesive film is covered with a substance-occlusive backing layer mad f a material that is poorly soluble in water or in the fluid secretions of the body cavity in which the film is

used. Examples of substance-occlusive poorly soluble materials that are safe for oral use include poly(dimethyl siloxane), poly(tetrafluoro ethylene), cellulose acetate, and copolymers of neutral methacrylic acid esters with one or both of methacrylic acid and diethylaminoethyl methacrylate. In a dental prosthesis adhesive film application, for example, the adhesive can be loaded with a flavoring or a mouth deodorant to act as a breath freshener, or with an antibacterial. Suitable flavorings, mouth deodorants, and antibacterials are known in the oral hygiene art. As the adhesive slowly dissolves, the agent is gradually released into the oral cavity.

Or, in a dental prosthesis adhesive film application, the adhesive can be loaded with a substance to be delivered transmucosally; in this configuration, the dental prosthesis works as an occlusive backing.

The water-soluble pressure-sensitive adhesives of the invention can be employed as an adhesive layer in a laminated device for diffusional delivery of an agent within a mucosa-lined body cavity. Such laminated devices can take any of a variety of forms, and may have just one layer in addition to the adhesive (such as the substance-occlusive poorly soluble layer described above, for example), or many additional layers.

Water-soluble pressure-sensitive adhesive films according to the invention can be made by other processes than described above. Where a press is used to form the film, for example, different temperatures may be used, according to the particular polymer composition.

For example, the molten polymer may be extruded through a slit die to form a film of the desired thickness; or it can be extruded or cast as a single film between release surfaces. In the latter case, the product can be cut to a shape appropriate to the particular application, and the release liners can be peeled away just prior to use.

It is to be understood that while the invention has been described in conjunction with the above embodiments, that the foreg ing description and examples are intended to illustrate and not limit the scope of the invention. Other

aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

CLAIMS

1. A water-soluble pressure-sensitive adhesive comprising a water-soluble polymer and a water-soluble plasticizer, said polymer having a T(g) or a T(m) greater than about 25°C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

2. The water-soluble pressure sensitive adhesive of claim 1 wherein said polymer has a T(g) or a T(m) greater than about 30°C.

3. The water-soluble pressure-sensitive adhesive of claim 1, said polymer comprising poly(vinyl pyrrolidone) and said plasticizer comprising glycerol.

4. The water-soluble pressure-sensitive adhesive of claim 3, said polymer further comprising hydroxy propyl cellulose.

5. The water-soluble pressure-sensitive adhesive of claim 3, comprising 95 - 40 weight % poly(vinyl pyrrolidone), 0 - 50 weight % hydroxy propyl cellulose, and 11 - 60 weight % glycerol.

6. The water-soluble pressure-sensitive adhesive of claim 3 further comprising hydroxy propyl cellulose.

7. The water-soluble pressure-sensitive adhesive of claim 3 wherein said poly(vinyl pyrrolidone) comprises less than about 34% by weight of said composition.

8. The water-soluble pressure-sensitive adhesive of claim 3 wherein said hydroxy propyl cellulose comprises about 20% - 50% by weight of said composition.

9. The water-soluble pressure-sensitive adhesive of claim 5, said glycerol being present in the range 30 - 50 weight %.

10. The water-soluble pressure-sensitive adhesive of claim 1, in film form.

11. A dental prosthesis adhesive, comprising the water-soluble pressure-sensitive adhesive film of claim 7, shaped to conform to a protion of the mucosal surface-contacting surface of the dental prosthesis.

12. A device for two-phase delivery of an active substance, comprising:

a) a first layer containing an effective amount of the active substance;

b) a second layer containing the active substance; and

c) an adhesive layer, wherein the first layer is positioned adjacent the adhesive layer, from which the active substance is released more slowly over wear time of the device as compared to the release rate of the second layer, and the second layer adjacent the first active-containing layer, from which the active is released more rapidly over a shorter initial wear time of the device as compared to the release rate of the first layer.

13. A method of delivering for the two-phase delivery of an active substance, the method comprising contacting the device of claim 12 with a surface of a subject.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02666

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 523/120; 524/43, 312; 428/40, 355; 424/435; 468, 472, 447, 448, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,373,036 (CHANG ET AL) 08 February 1983, See columns 2-3, 6 and 12	1-11
Y	US, A, 4,713,243 (SCHIRALDI ET AL) 15 December 1987, column 4, lines 32-40.	1-11
Y	JP, A, J63171565 (SEKISUI CHEM IND KK) 15 July 1988, See entire doucment.	1-11
Y	JP A, J63174660-A (SEKISUI CHEM IND KK) 19 July 1988, See entire docment.	1-11
X	US, A, 5,271,940 (CLEARY ET AL) 21 December 1993, See entire docment.	12-13
X,P	US, A, 5,455,043 (FISCHEL-GHODSIAN) 03 October 1995. See enitre docment.	12-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 MAY 1996	11 JUL 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAVONDA R. DEWITT Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02666

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,186,938 (SABLOTSKY ET AL) 16 February 1993, See entire document.	12-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02666

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-11, drawn to a pressure sensitive adhesive.
Group II, claims 12-13, drawn to a two-phase delivery device.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02666

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 6/00; C08L 1/26; C08K 5/10; A61F 13/02; B32B 7/12, 15/04, 11/00, 9/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

523/120; 524/43, 312; 428/40, 355; 424/435; 468, 472, 447, 448, 449